SAMANTHA'S STORY

SEVERE COMBINED IMMUNODEFICIENCY (SCID) & NEWBORN SCREENING

Isaac – 3 ½ years

"You're fired!!"

Samantha born August 4, 2009

Newborn screening tests provided in Oklahoma at the time came back normal.

Eye infection at 8 days old, but otherwise appeared healthy!

4 months old

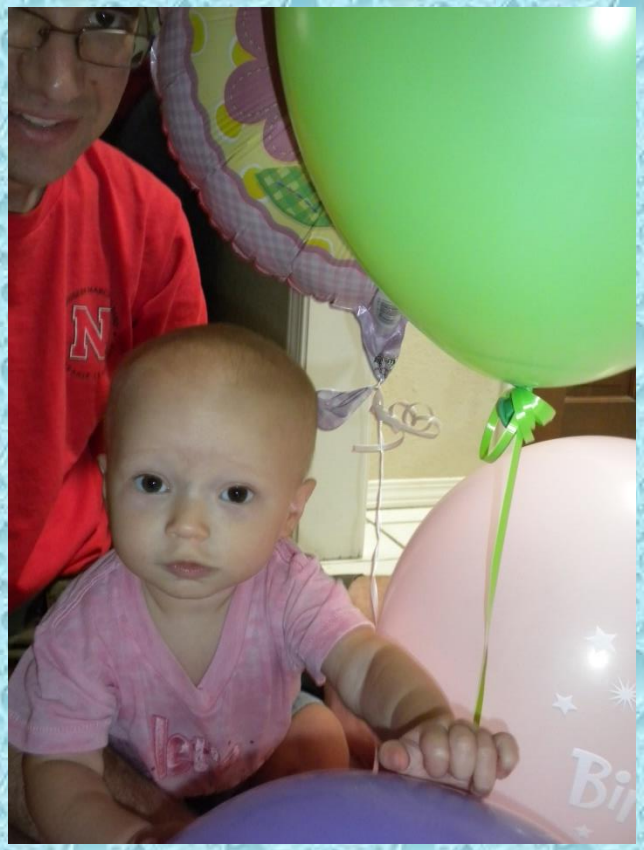
Height and weight =

Head size =

Decreased milk production???

Samantha the Exterminator

First Birthday!



Endocrine system? Diagnosed with hypothyroidism… but not present at birth???

15 months old

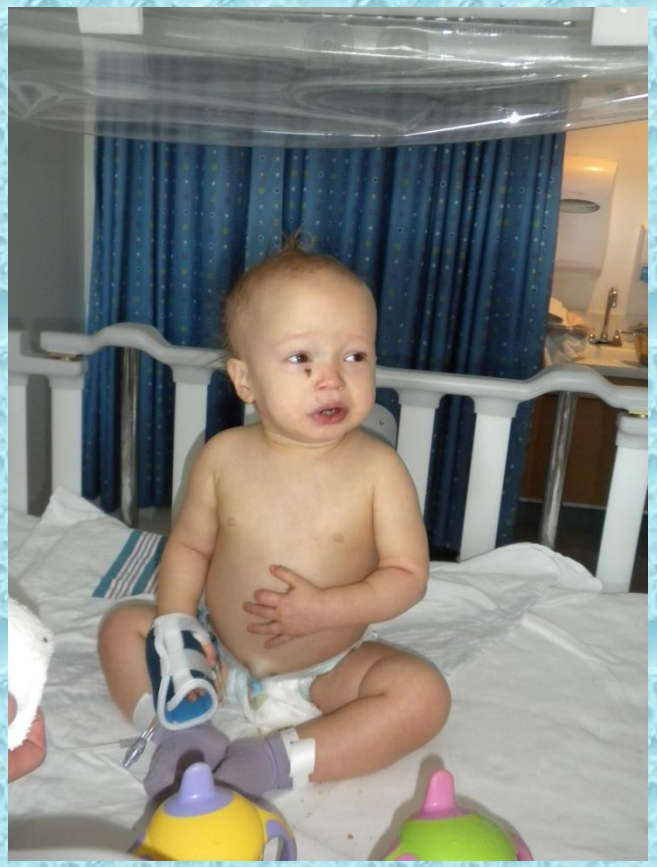
Hematologist unsuccessful at diagnosing, too!!

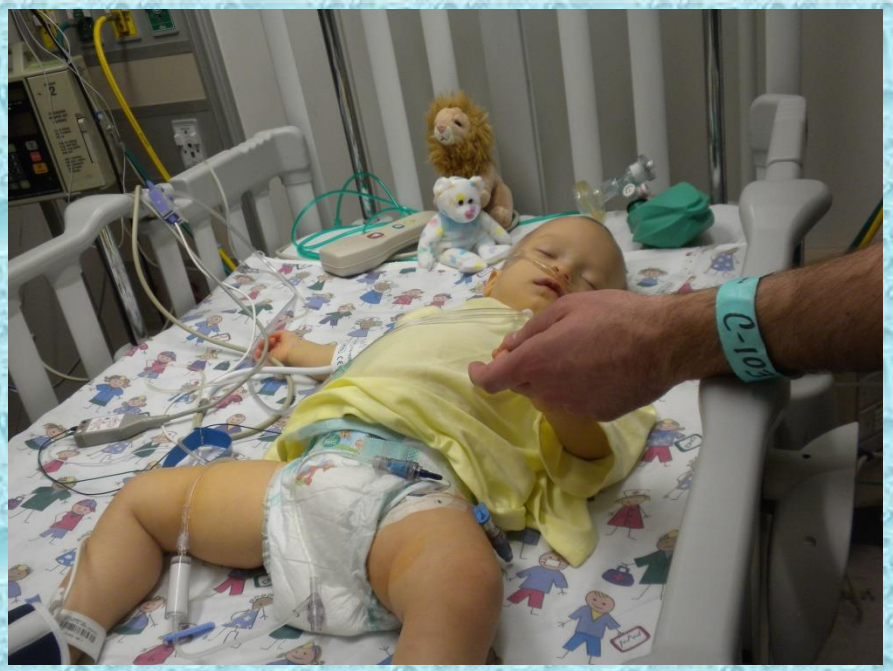
Samantha Walks!

Mmm…Lasagna!

Sick at home

Saint Francis Children's Hospital in Tulsa, OK





Five viral infections, debates amongst several specialists, and STILL no diagnosis!!

Cincinnati

Police Women of Cincinnati (2015)

The "Bubble Boy" – David Vetter

Dotinga (2006)

David taking some of his first steps outside of hospital isolation "bubble"

BAYLOR COLLEGE OF MEDICINE ARCHIVES

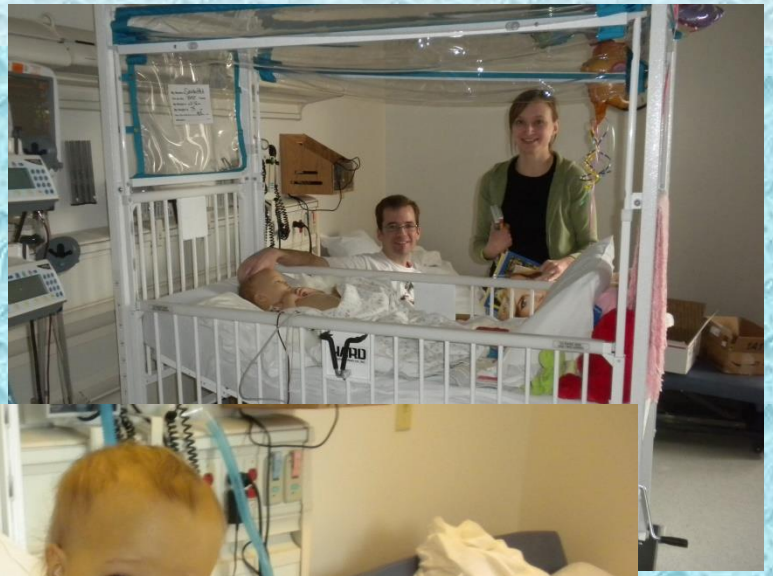
Public Broadcasting Service (2006)

SCID: Defined

"**the most serious primary immunodeficiency disease.** Affected infants lack T lymphocytes, the white blood cells that help resist infections due to a wide array of viruses, bacteria and fungi. Babies with SCID appear healthy at birth, but **without early treatment, most often by bone marrow transplant from a healthy donor, these infants cannot survive.**"

Immune Deficiency Foundation (2010)

Cincinnati Children's Hospital



CMX001 as Therapy for Severe Adenovirus Infections in Immunocompromised Pediatric Patients: Single Center Experience in 5 Patients

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Background

▪Adenovirus is a serious and often fatal complication in immunocompromised patients. The incidence of adenovirus infections in increasing, likely due to the use of lymphocyte-targeted conditioning, umbilical cord blood as stem cell source and T cell depleted allografts. Estimates of the incidence of adenovirus infection in HSCT recipients range from 5-47% with the highest rates reported in the first 100 days post transplant. Mortality rates of up to 70% have been reported.

•Cidofovir has been used to treat adenoviral infections with variable efficacy and is associated with significant toxicity, especially renal and possible marrow toxicity. CMX001 is an orally bioavailable lipid conjugate of Cidofovir is under investigation for the prevention of adenovirus disease.

CMX001

•CMX001 (manufactured by Chimerix, Inc.) is an orally bioavailable lipid-conjugate of the nucleotide analog, cidofovir.
•Lipid conjugate allows for oral administration and enables rapid uptake of CMX001 into cells resulting in higher intracellular levels compared to cidofovir.
•Inside target cells, the lipid side chain of CMX001 is cleaved to yield free cidofovir which is then converted to the active antiviral agent, cidofovir-diphosphate, by a 2 step phosphorylation process.

Methods

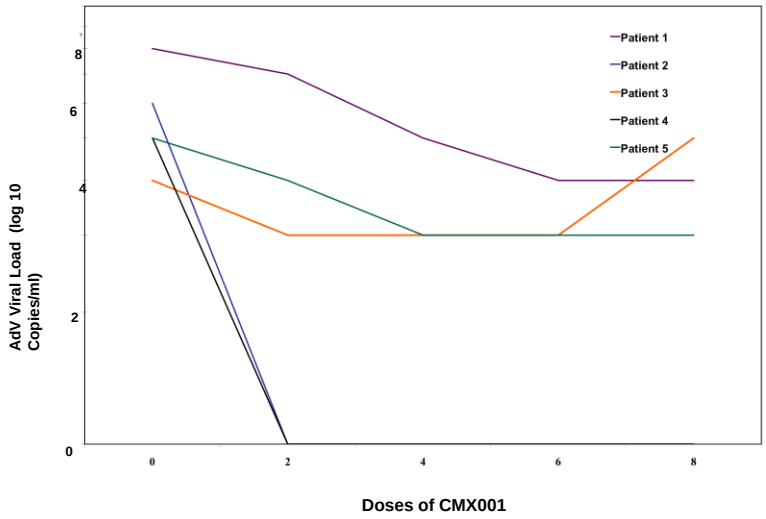
- Five patients were treated with CMX001 between February 2011 and August 2011.
- Two patients were treated under EIND approval and 3 patients were treated on the expanded access protocol (CMX001-350).
- Median age of the patients was 1.9 years (range 1.5 - 11.8 yrs).
- HSCT patients received a reduced intensity preparative consisting of Alemtuzumab, Fludarabine and Melphalan.
- Stem Cell Source was Unrelated Donor Bone Marrow.
- GVHD prophylaxis was cyclosporine and methylprednisolone.
- Data was available for > 4 weeks of treatment .
- Virologist Response (VR) was defined as 1log drop in copy number from baseline or undetectable ADV DNA by PCR in plasma.
- Patient characteristics are shown in Table 1 .

Table 1: Patient Characteristics

Patient	Diagnosis	Age (yrs)/Sex	Days post HSCT of ADV Detection	Sites of ADV Infection	Day O Viral Load (copies/ml)	Dose of CMX001	Adverse Events	Current Status/ Followup (months)
1	SCID	1.5/F	N/A	Blood and Stool	148 million	10 doses of 4 mg/kg/dose BIW	None	Died of Disseminated Aspergillosis
2	SCID due to RAG2 mutation	1.2/F	- 7	Blood and Stool	1.2 million	11 doses of 4 mg/kg/dose BIW	None	Alive and Well/8 months
3	HLH	11.8/M	300	Blood, Stool and Nasal Secretions	32,000	1 dose of 4 mg/kg/dose BIW then 11 doses of 2 mg/kg/dose BIW	Diarrhea	Died of Progressive Bronchiolitis Obliterans
4	XLP/MDS	6/M	70	Blood and Stool	89,000	5 doses of 4 mg/kg/dose BIW then 32 doses of 2 mg/kg/dose BIW	Diarrhea	Alive and Well/ 7 months
5	XLP	2/M	5	Blood and Stool	102,000	10 doses of 2 mg/kg/dose BIW	None	Died of Pulmonary TMA

SCID: Severe Combined Immunodeficiency; FHL: Familial Hemophagocytic Lymphohistiocytosis; MDS: Myelodysplastic Syndrome; XLP: X-Linked Lymphoproliferative Disorder; BIW: Twice a week; TMA: Thrombotic Microangiopathy

Figure 1: Virologic Response to CMX001



Results

•Adenovirus Disease was diagnosed at a median of 38 days (range -7 to 300) after HSCT in the transplant patients.

•Patient 1 presented with disseminated ADV infection at the time of her initial SCID diagnosis.

•All patients received IV Cidofovir for a median of 27 days (range 22-47) prior to starting CMX001.

•Four of five patients (80%) had at least a 1 log decrease in viral load after 2 doses of CMX001 (1 week of therapy).

•VR was seen in all patients.

•Four patients received doses exceeding those currently being studied. No adverse events felt secondary to CMX001 were observed in those patients who received the 4 mg/kg/dose dosing.

Adverse Events

• Two patients developed diarrhea that was likely related to CMX001 while receiving the 2 mg/kg/dose BIW. Diarrhea resolved when CMX001 was held and both patients were able to resume therapy without a recurrence of GI symptoms.

•Patient 3 had an increase in AdV viral load while his CMX001 was held for diarrhea. When restarted, he again had VR.

•No renal or marrow toxicity was seen in these patients.

•No other Adverse Events attributable to CMX001 were observed.

Discussion

•Our data demonstrate that CMX001 has efficacy against Adenoviral infections.

•Virologic Response was rapid with most patients have a 1 log decrease in viral load after 2 doses of CMX001.

•A favorable safety profile was seen.

•In this critically ill group of patients, morbidity was high which may reflect that CMX001 is an investigational medicine and was not used as first line therapy for adenoviral infections in our institution for these patients.

•Further clinical studies with CMX001 in patients with Adenoviral infections should be undertaken.

Conflict of Interest Statement

•There are no relevant conflicts of interests to disclose.

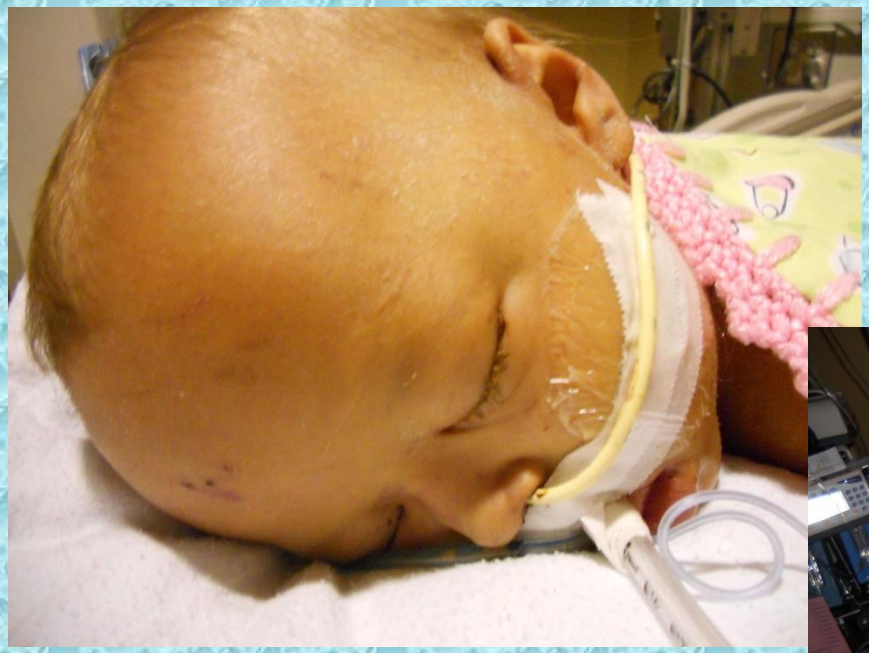
Grandma & Grandpa

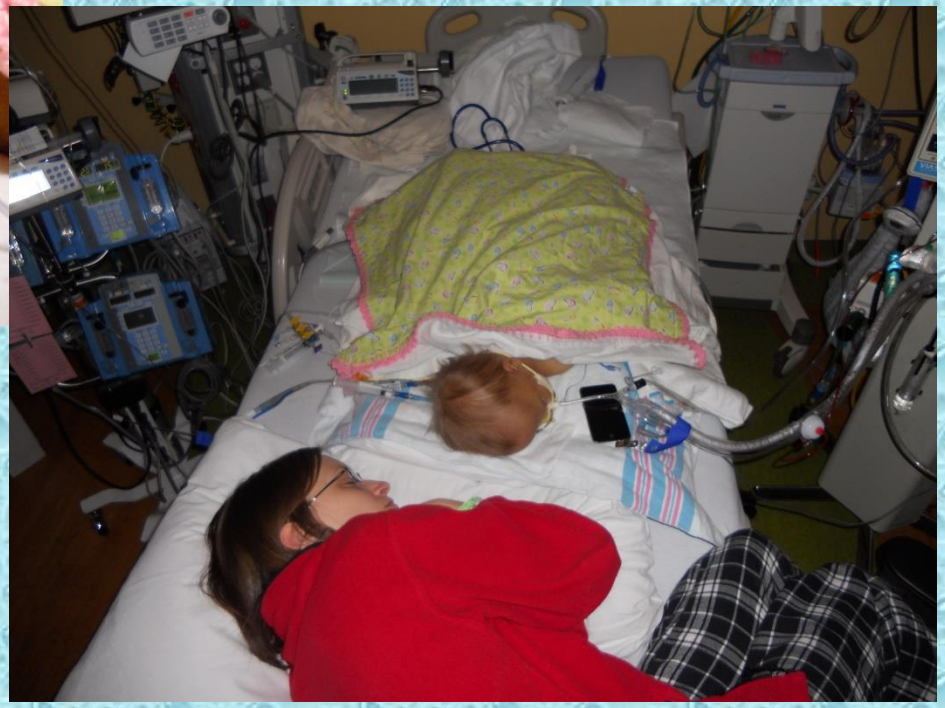
Ronald McDonald House: Our Oasis

Third largest RMH in the country, complete with an isolation wing for families like ours.

Our friendly greeter at the end of a long day.

Her final days spent in the PICU





Lightning can Strike Twice

- 6 months after Samantha died, carbon copy case from our small Oklahoma town
- Same pediatrician, same hospitals, went to Cincinnati – followed in Samantha's footsteps
- Because it was caught early, could go to a BMT
- Natalie is now back home, healthy and leads a mostly normal childhood (although they still do lots of hand washing!)

NBS saves lives, saves cost!

- **SCID curable through a bone marrow transplant if caught early enough**
  - **94% survival if BMT within first 3.5 months**
  - **70% or lower if no BMT in first 3.5 months**

- **Clear cost-benefit (saves states money and lives)**
  - **Samantha's treatment over $1.2 million in just 2 months (no BMT)**
  - **SCID screening for whole state of ND/year: $79,000**
  - **1 Medicaid baby/3 years @ $250,000 (with BMT) + $79,000 < Samantha's total hospital bill**

Chan, Davis, Pai, Bonilla, Puck, & Apkon (2011)

Thank You!!

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